



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>4</sup> : <b>A61K 35/20, 37/02, C07K 3/24 C07K 15/00 // A61K 7/48</b>		A1	(11) International Publication Number: <b>WO 86/ 00525</b> (43) International Publication Date: 30 January 1986 (30.01.86)		
(21) International Application Number: <b>PCT/HU85/00042</b>		(81) Designated States: AT (European patent), AU, BE (European patent), BG, BR, CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, RO, SE (European patent), SU, US.			
(22) International Filing Date: 12 July 1985 (12.07.85)					
(31) Priority Application Number: 2751/84					
(32) Priority Date: 13 July 1984 (13.07.84)					
(33) Priority Country: HU		Published <i>With international search report.</i>			
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(54) Title: PROCESS FOR THE PREPARATION OF A PHARMACEUTICAL COMPOSITION INFLUENCING THE TISSUE METABOLISM AND HAVING A REGENERATING ACTION					
(57) Abstract					
<p>Preparation of a pharmaceutical composition influencing the tissue metabolism and having a regenerating action, which comprises adding crystal water-free potassium aluminium sulphate to a milk kept at a temperature above 90°C, then separating the solid material from the solution after the segregation of the obtained dispersion and optionally adding an aromatizing, preserving or colouring agent to the solution. The composition of the invention has an excellent regenerating action on the skin, muscle and bones. The metabolism disturbances of the tissues are also abolished, whereby the improvement of e.g. vascular stenoses can be achieved.</p>					

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PROCESS FOR THE PREPARATION OF A PHARMACEUTICAL COMPOSITION  
INFLUENCING THE TISSUE METABOLISM AND HAVING A REGENERATING  
ACTION

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Technical field

The invention relates to a process for the preparation of a pharmaceutical composition influencing the tissue metabolism and having a regenerating action, the effect of which mainly appears in promoting the tissue regeneration and assuring the tissue metabolism; however, this composition is also useful, inter alia for abolishing spastic muscle states and for relieving pain.

It has unexpectedly been recognized that a composition having the effects mentioned above can be obtained by adding crystal water-free potassium aluminium sulphate to a milk kept at a temperature above 90 °C, then separating the solution from the solid material after the segregation of the obtained dispersion and optionally adding aromatizing, preserving and colouring agents to the solution.

Disclosure of the invention

Based on these facts, the invention relates to the preparation of a pharmaceutical composition influencing the tissue metabolism and having a regenerating action. The process of invention comprises adding crystal water-free potassium aluminium sulphate to a milk kept at a temperature above 90 °C, separating the solution from the solid material after the segregation of the dispersion thus obtained and optionally adding aromatizing, preserving and colouring agents to the solution.

It can be supposed that the active agent of the composition prepared by using the process of invention is the whey obtained in the way described above. Although no mode of action is postulated, it is supposed that for the

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tissue metabolism the products, the appropriate concentration of which is indispensable for the tissue regeneration in a given period, are provided by the amino acid content of the whey.

5 It has been proved by investigating the acid-base balance and the gas tension parameters as well as the changes in the whole resting respiratory function of the human body that the composition is rapidly and significantly absorbed through the skin. The acid-base balance is  
10 shifted to a moderately metabolic acidosis which is then later shifted back to a mild alkalosis as a consequence of the amino acid metabolism.

15 In addition to the general action mentioned above, the function of the respiratory system also becomes more economical and the capacity thereof is enhanced by the composition of the invention.

20 All these observations indicate that by using the composition of the invention metabolizing acidic substances, which are indispensable for a tissue regeneration, can be advantageously introduced into the organism through the skin, that is, in a fully new way. These acidic substances exert an advantageous influence on the interior homeostasis of the cells and of the intercellular substance through the acid-base balance. The substances required for the tissue 25 regeneration are directly provided to the cells by the amino acid content of the composition of invention through a direct diffusion, i.e. without the intervention of the systemic blood circulation. As the application through the skin of such substances is unknown to our best knowledge, 30 a comparison to known oral or parenteral compositions is void of any sense.

As starting materials of the process of invention, fatty cow milk can preferably be used, however a less fatty cow milk or e.g. goat's milk can also be used.

35 For treating the milk, crystal water-free potassium

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aluminium sulphate, suitably alum heated at a temperature between 300 °C and 400 °C is used.

According to a practical embodiment of the process of invention, 1.6 to 2.1 g, depending from the fat content of the milk, of crystal water-free potassium aluminium sulphate are suitably added portionwise to 1 litre of milk, preferably at the boiling point of the milk, whereby the casein and fatty materials are precipitated. After some time, the supernatant becomes substantially pure and can be separated. For this purpose filtration and/or centrifugation are suitably used.

On carrying out the process of invention with a crystal water-free potassium aluminium sulphate obtained by heating natural or amorphous alum at 250 °C to melting and then up to the re-solidification /a spongy structure being formed/, after the segregation of the dispersion a completely pure solution is obtained, whereby a filtration becomes unnecessary.

The thus-obtained solution is actually suitable for a therapeutical use, but an aromatizing agent should be added for masking the inconvenient odour of the materials arising from the milk and a preserving agent has to be mixed in for preventing the decomposition of the materials arising from the milk. A colouring agent may also be added optionally to the composition for promoting the acceptability of the use thereof.

According to a preferred embodiment of the process of invention, an extract arising from a medicinal plant /herb/ is used as an aromatizing agent, whereby the inconvenient odours are fully masked and simultaneously, the medicinal plant extract may have an own advantageous action. The aqueous extract of woundwort /Solidago gigantea Ait. or Solidago serotina/, of Glechoma hederacea L., and of herb-ovv /Teucrium chamaedrys L./, or of silver-weed /Potentilla anserina L./ together with the above-mentioned

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three medicinal plants may suitably be used as aromatizing agent. The aqueous extract can be prepared in a manner known in the art, suitably by boiling a mixture containing an 1:1 ratio by weight of the medicinal plants 5 with water for 5 minutes and queezing the juice obtained through a press.

Instead of the medicinal plant extracts mentioned above, any other aromatizing agent commonly used in the pharmaceutical industry, such as pine, hay or orange 10 aroma, may be used as aromatizing agent.

Similarly, preservatives commonly used for preparing pharmaceutical compositions may be used as preserving agents in the process of the invention. It is suitable to use ethanol, preferably pure ethanol of 96 %. Within a 15 large-scale production, e.g. 70 % by volume of whey, 23 % by volume of pure 96 % ethanol and 7 % by volume of a medicinal plant extract /optionally containing 96 % ethanol, suitably 1 litre of pure 96 % ethanol for each 4 litres of the aqueous extract/, calculated for 1 litre 20 of the pharmaceutical composition, may be used. Instead of ethanol, other preservatives may also be employed, by the use of which the whey liable to fermentation is preserved, the amino acid contents are not damaged, the treated skin is not irritated and the preserving effect is exerted 25 even if the composition of the invention comes into contact with the skin.

#### Industrial applicability

The compositions prepared by using the process of 30 the invention are utilized for pharmaceutical purposes as follows.

Suitable ready-for-use formulations of the compositions of the invention are the liniment, lotion and spray which may be prepared in a manner well-known in the 35 pharmaceutical industry, optionally by employing the

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additives commonly used for these types of pharmaceutical formulations.

Obviously, the amount and manner of the active substances used for a therapeutic purpose are dependent 5 on a number of factors such as the status of the patient, the effectivity and concentration of the active substance as well as the formulation.

The composition of the invention is suitably applied by infraction to the body part to be treated daily 2 to 5 10 times.

An optimum effect on diseases caused by vascular stenoses is provided by three treatments per day.

The treatment is carried out as follows.

The composition of the invention is applied to the 15 surface to be treated by hand or in a spray form. After absorption, the treatment is repeated and, after the second absorption, a third infraction is made. It is essential to keep the surface to be treated wet for about 10 minutes. As mentioned above, this treatment can be 20 accomplished daily 3 times.

In the course of a rehabilitation after knee operations, the use of lotions is convenient. In this case, it is suitable to pour the agent daily 5 to 10 times onto the body part covered with a compress.

25 The main therapeutic effects of the compositions prepared according to the process of the invention are as follows.

1. On the basis of the mode of action described above, it can be stated that the cellular activity is 30 stimulated and normalized by the amino acids introduced by the composition into the tissues, as the substances required thereto are provided in the appropriate quantity, time and manner.

2. A therapeutic chain reaction in several directions 35 is started in the organism as a consequence of the

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regenerated advantageous cellular activity, whereby a rapid improvement or recovery is achieved in the following cases:

5        a/ A regenerating action on the skin, muscle and bones: the restoration of ulcers, gangrenes and other wounds, as well as a rapid rehabilitation after muscle lesions, cartilage- and syndesmoplastic operations and the like;

10      b/ Abolishment of metabolic disturbances: a restoring effect in vascular stenoses is achieved by the improvement of the metabolic economy in the musculature of the extremities, i.e. the metabolic disturbances thereof are abolished, while the blood circulation remains unchanged and the deficient states get a balance /in the cases of 15 arteriosclerosis obliterans, endarteritis obliterans and the consequences thereof/;

15      c/ The composition of the invention shows an outstanding analgesic effect: the pain is abolished or alleviated to a minimum at 10 to 15 minutes after the 20 infliction.

#### Modes of carrying out the invention

The invention is illustrated by the following non-limiting Examples.

25

#### Example 1

Commercially available crystalline alum /potassium aluminium sulphate;  $KAl(SO_4)_2 \cdot 12H_2O \cdot 7$ / is heated at a temperature between  $300^{\circ}C$  and  $400^{\circ}C$ , whereby the alum 30 becomes free from the crystal water, then it melts and re-solidifies. A spongy-structured material is obtained.

Fatty milk is heated to the boiling point and 1.8 g of the above-described spongy alum, calculated for 1 litre of milk, are added under continuous boiling. The mixture 35 is then boiled for 10 minutes and after the complete

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precipitation of casein, the supernatant solid materials are removed from the milk surface by using a filter bag to give an opalescent, transparent liquid. After cooling down of the filtrate to a temperature between 35 °C and 5 40 °C, 1 litre of 96 % ethanol, calculated for each 4 litres of the filtrate, is added.

A decoction is prepared from 250 g of woundwort, 250 g of Glechoma hederacea L. and 250 g of herb-ovv with 6 litres of water during 5 minutes, whereupon the juice of 10 the medicinal plants are queezed through a press to give a decoction of about 4 litres. Each 4 litres of this decoction is mixed with 1 litre of 96% ethanol.

75 ml of the decoction containing ethanol are added to 925 ml of the filtrate prepared as described above.

15

Example 2

The process described in Example 1 is followed, except that 200 g of woundwort, 200 g of Glechoma hederacea L., 200 g of herb-ovv and 200 g of silver-weed are used as 20 medicinal plants.

The results of the pharmacological study on the compositions prepared according to the process of invention are described in the following Test Examples.

25

Test Example 1

The action of the composition prepared as described in Example 1 was investigated on 60 patients suffering from vascular stenosis /arteriosclerosis obliterans or endarteritis 30 obliterans/. Simultaneously, a control group consisting of 25 patients was treated by a traditional method commonly used in the medicinal practice and a control group consisting of 25 patients was treated with a liquid having the same colour and odour as that of the agent but containing 35 no whey /negative control/. The agent was applied daily

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3 times to the affected body parts by infarction as described above. No improvement was stated on the negative control group; a little improvement was observed on the patients treated by the traditional method; and an amelioration 5 of the clinical symptoms in the temperature of the extremity and in the restoration of trophic ulcerations were observed in all cases on the patients treated with the composition of Example 1. Thus, the distance of claudication was increased from 100 meters or 200 meters 10 to an infinite value, i.e. the patient became free from complaints, the frequent nocturnal sura spasms were abolished and the demarcation and drying of pyelous ulcers, crust formation, detachment of the crusts and the epithelium formation were observed even on aged patients.

15 In the course of the acute action of the composition of Example 1, the skin temperature was decreased by 3 to 4 °C, then it warmed back gradually and reached the original value as measurable on healthy individuals within 50 to 60 minutes. It was observed on using the composition of 20 Example 1 for the treatment of vascular stenoses that the temperature of the sick side was lower than that of the healthy one. The above temperature decrease was observed also here, but it is considered to be very significant that the temperature of the sick extremity did not increase only 25 to the starting value, but to a temperature identical with that of the healthy side, i.e. to a temperature higher than the starting value. When the agent was chronically applied, the resting skin temperature of the sick extremity was increased by 2 °C on using infarctions daily 5 times 30 for 2 weeks. An oscillometric examination was made on the patients to decide if the agent had any effect on the vascular stenosis or the tissue metabolism were improved with the retention of an unchanged vascular lumen. The oscillometric value was increased on the most part of the 35 patients /over the ankle, below and over the knee/; however

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the conclusion was made that the status of the blood vessel was actually not influenced by the agent and the excellent action was achieved by an improvement in the economy of metabolism, while the blood circulation remained unchanged.

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Test Example 2

The composition prepared according to Example 1 was used on 17 patients within the course of rehabilitation following a plaster-bandage used 6 weeks after knee operations /cartilage and syndesmoplasty/. Here, a compress was used as described above. It was stated that the severe pain appearing at the initial movements was significantly or nearly completely alleviated and the enhanced muscular tonus was also abolished. Thus, the restoration of the passive motion limits of the articulation was enhanced within a very short period and the tiredness, known as muscular strain, did not appear in the extremity during the active curative gymnastics. As a consequence, the rehabilitation period was shortened by 20 to 50 % and the troubles connected with the movements of the patients were significantly reduced.

These effects were not observed on 10 control patients.

25

Test Example 3

The action of the composition prepared as described in Example 1 was studied on 14 patients /as compared to 8 control patients/ on such types of neuritic diseases, where the irritation of a nerve was caused by a change of the condition of the musculature /functional neuritis/. In these cases, a trophic trouble was observed on the supplied area and a local blood circulation trouble was also found. The extent of the condition change was judged from the temperature of the sick area: the cooler was this area, the more pronounced was considered the change. The

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agent was applied to the affected area daily 5 times by infarction for 2 weeks. After ending the treatment, the collateral difference of 3 to 4 °C disappeared.

5           Test Example 4

In addition to the general action of the composition prepared as described in Example 1, it was observed that the respiratory mid-position was shifted to a lower level on all treated patients, i.e. the inspiratory reserve 10 volumen was increased, while the expiratory reserve volumen was decreased. Thus, it has been proved that the composition exerted a very advantageous effect on the economy of the respiratory system. The maximum ventilation volumen was increased, a fact showing that the capacity of the respiratory 15 system was also enhanced in addition to the economizing effect.

In the course of our investigations the following devices have been used:

1. Skin thermometer /Servintern Rolitron licence  
20 "Thermini 130"/;
2. Thermovision equipment /AGA thermovision 780 type/.

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What we claim is:

1. A process for the preparation of a pharmaceutical composition influencing the tissue metabolism and having  
5 a regenerating action, which comprises adding crystal water-free potassium aluminium sulphate to a milk kept at a temperature above 90 °C, then separating the solid material from the solution after the segregation of the obtained dispersion and optionally adding an aromatizing, preserving or colouring agent to the solution.
- 10 2. A process as claimed in claim 1, which comprises using 1.6 to 2.1 g of crystal water-free potassium aluminium sulphate, calculated for one litre of milk.
- 15 3. A process as claimed in claim 1 or claim 2, which comprises using alum heated at 300 to 400 °C as crystal water-free potassium aluminium sulphate.
- 20 4. A process as claimed in claim 1 or claim 2, which comprises using fatty cow milk as milk.
- 25 5. A process as claimed in any one of the claims 1 to 4, which comprises using a medicinal plant extract as aromatizing agent.
- 30 6. A process as claimed in claim 5, which comprises using an aqueous extract of woundwort /Solidago gigantea Ait. or Solidago serotina/, Glechoma hederacea L. and herb-ovy /Teucrium chamaedrys L./ as a medicinal plant extract.
- 35 7. A process as claimed in claim 5, which comprises using an aqueous extract of woundwort, Glechoma hederacea L., herb-ovy and silver-weed /Potentilla anserina L./ as a medicinal plant extract.
8. A process as claimed in any one of the claims 1 to 7, which comprises using ethanol as a preservative.
- 35 9. Pharmaceutical compositions whenever prepared by the process according to any of claims 1-8.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 85/00042

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC4: A 61 K 35/20, A 61 K 37/02, C 07 K 3/24, C 07 K 15/00  
 //A 61 K 7/48

## II. FIELDS SEARCHED

Minimum Documentation Searched \*

Classification System	Classification Symbols
Int.Cl. <sup>4</sup> :	A 61K 35/20, 35/12, 37/02, 33/06, 33/14; C 07 K 15/00, C 07K 15/24, 3/02, 3/24; A 61 K 7/48.

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched \*

AT

## III. DOCUMENTS CONSIDERED TO BE RELEVANT\*

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages ***	Relevant to Claim No. **
A	AT, B, 41 810 (CASEIN AND MILK INDUSTRIES LIMITED), 11 April 1910 (11.04.10), see claim; page 1, lines 11-34.	(1)
A	GB, A, 6 247/A.D. 1908 (CARL ALBRECHT BAECHLER), 24 September 1908 (24.09.08), see claim 1; page 1, lines 21-43; page 2, lines 1-6, 14-29.	(1)
A	US, A, 2 721 861 (LAURENE O. PATERSON), 25 October 1955 (25.10.55), see claims 1-5; column 3, lines 8-14; column 5, lines 7-14, 23-27.	(1)
A	DE, A1, 3 001 300 (SOCIETE DES PRODUITS NESTLE S.A.), 24 July 1980 (24.07.80), see claims 1-4; page 3, lines 4-11; page 6, lines 8-16.	(1)
A	DE, C, 959 219 (MERZ & CO.), 28 February 1957 (28.02.57), see claims 1-4; page 1, lines 1-6; page 2, lines 30-44.	(1)

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## IV. CERTIFICATION

Date of the Actual Completion of the International Search

14 October 1985 (14.10.85)

Date of Mailing of this International Search Report

17 October 1985 (17.10.85)

International Searching Authority

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## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	DE, A1, 3 029 263 (DORIS COSMETIK WERK MARTIN EBERLE & CO), 19 March 1981 (19.03.81), see claims 1-4; page 2, lines 18-22.	(1)
A	GB, A, 2 052 979 (PIERRE-JEAN ASSIER DE POMPIGNAN, SERGE LIOTET), 4 February 1981 (04.02.81), see abstract; claims 1,2; page 1, lines 1-55.	(1)
A	EP, A1, 0 009 464 (VERBAND AARGAVISCHER KÄSEREI- UND MILCHGENOSSENSCHAFTEN), 2 April 1980 (02.04.80), see abstract; claims 1-3.	(1)
	-----	

Anhang zum internatio-  
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über die internationale  
Patentanmeldung  
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AT-B - 41 810	11/04/1910	None	
GB-A - 6 247/A.D. 1908	24/09/1908	None	
US-A -2 721 861	25/10/1955	None	
DE-A1-3 001 300	24/07/1980	AR-A1- 219 654 BE-A1- 881 154 CA-A1-1 131 561 CH-A - 641 345 FR-A1-2 446 634 FR-B1-2 446 634 GB-A1-2 046 591 GB-B2-2 046 591 JP-A2-55-098110 NL-A -8 000 249 US-A -4 463 017	29/08/1980 15/07/1980 14/09/1982 29/02/1984 14/08/1980 18/06/1982 19/11/1980 30/03/1983 25/07/1980 18/07/1980 31/07/1984
DE-C - 959 219	28/02/1957	None	
DE-A1-3 029 263	19/03/1981	AT-A - 5 695/79 AT-B - 363 193	15/12/1980 10/07/1981
GB-A -2 052 979	04/02/1981	BE-A1- 883 935 CH-A - 644 269 DE-A1-3 024 623 FR-A1-2 460 135 FR-B1-2 460 135 JP-A2-56-053612	16/10/1980 31/07/1984 22/01/1981 23/01/1981 19/11/1982 13/05/1981

FCT/HU 85/00042

GB-A -2 052 979	04/02/1981	NL-A -8 003 802 US-A -4 342 747	06/01/1981 03/08/1982
EP-A1-0 009 464	02/04/1980	CH-A - 635 512	15/04/1983

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